# VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF OPIOID THERAPY FOR CHRONIC PAIN

## Guideline Summary

***RECOMMENDATIONS WITH THE HIGHEST EVIDENCE: The highest evidence for recommendations is A, defined as "a strong recommendation based on randomized controlled trials that the intervention is always indicated and acceptable."***

1. Assessment of function should include: **[R=A]**
   - Cognitive function (attention, memory, and concentration)
   - Employment
   - Enjoyment of life
   - Emotional distress (depression and anxiety)
   - Housework, chores, hobbies, etc.
   - Sleep
   - Mobility
   - Self-care behaviors
   - Sexual function
2. Consider the use of other treatment approaches (supervised therapeutic exercise, biofeedback, and cognitive behavior approaches), which should be coordinated with the opioid therapy. **[R=A]**
3. For continuous pain, an agent with a long duration of action, such as controlled-release morphine or methadone is recommended. **[R=A]**
4. A trial should be considered for either nociceptive or neuropathic pain. Neuropathic pain often requires higher doses of medication than nociceptive pain. **[R=A]**
5. During titration, once a pain relief response has been achieved at a particular dose, the time interval can be determined by repeating this same dose when the level of pain begins to rise. **[R=A]**
6. Adverse effects may often be minimized by either modifying the dose during titration or rotating to a different opioid agent. **[R=A]**
7. The following adverse effects are the most common. A prophylactic treatment and specific patient education should be provided together with initiation of therapy. Symptomatic treatment should be augmented with dose modification and/or opioid rotation.

   a. **Nausea and vomiting** - Consider prophylactic antiemetic therapy. **[R=A]**
8. Consider one or more of the following adjustments in therapy to Achieve Stable Pain Relief:
   - Increase dose titration. Increase dose by 25-100%. An increase of less than 25% is not appropriate **[R=A]**
   - To ensure that the full effect from a dosage change has been manifest and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every 5 half lives **[R=A]**
   - If possible, titrate only one drug at a time, while observing the patient for additive effects. Inappropriate medications should be tapered while initiating an appropriate pharmacologic regimen **[R=A]**
   - Medication may be increased until limited by adverse effects or clear evidence of lack of efficacy **[R=A]**

VA access to full guideline: http://www.oqp.med.va.gov/cpg/cpg.htm
DoD access to full guideline: http://www.qmo.amedd.army.mil/

*June 2003*

Sponsored & produced by the VA Employee Education System in cooperation with the Offices of Quality & Performance and Patient Care Services and the Department of Defense.

# VA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF OPIOID THERAPY FOR CHRONIC PAIN

## Guideline Summary

## KEY ELEMENTS

1. Use of opioid therapy when other pain therapies are inadequate.
2. Determine goal of therapy with patient and caregivers.
3. Opioid therapy for chronic pain has an average decrease in pain score of 30%, with a similar incidence of significant adverse effects.
4. Assure safety—do no harm. Optimize therapy through trial and titration based on assessment.
5. Obtain comprehensive assessment of the patient before initiating therapy.
6. Regularly assess adverse effects, adherence to treatment plan, efficacy, and satisfaction.
7. Develop an opioid therapy agreement with the patient to define responsibilities and expectations of both the patient and the provider.
8. Educate patient about therapy, adverse effects, and withdrawal.
9. Apply multimodal adjunctive therapy as indicated by the patient and the disease process.
10. Accurate documentation of all prescriptions, agreements, and assessments.
11. Refer and/or consult with pain clinic or substance use specialty when needed.
12. Discontinue opioid therapy when it is not indicated.

## VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain

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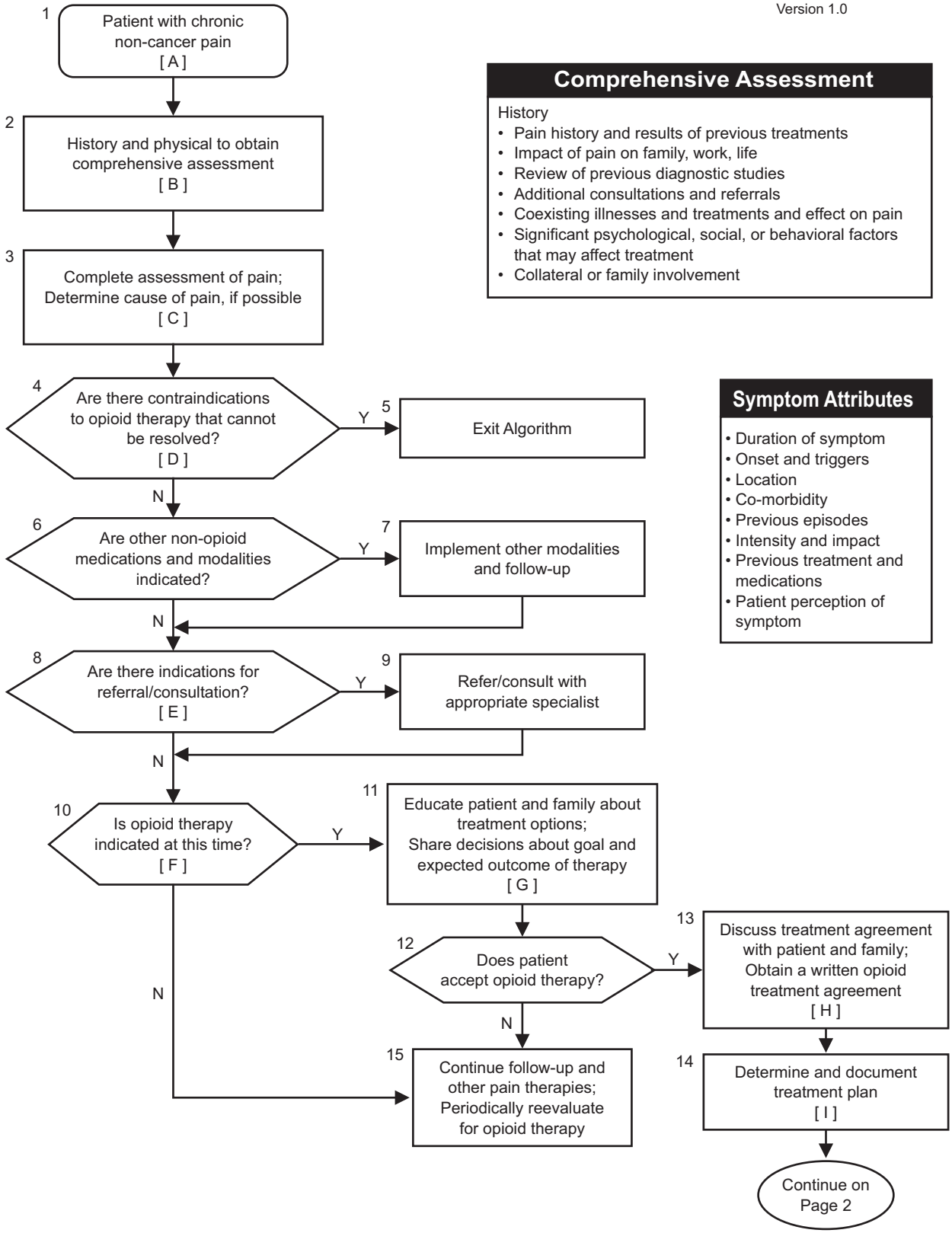

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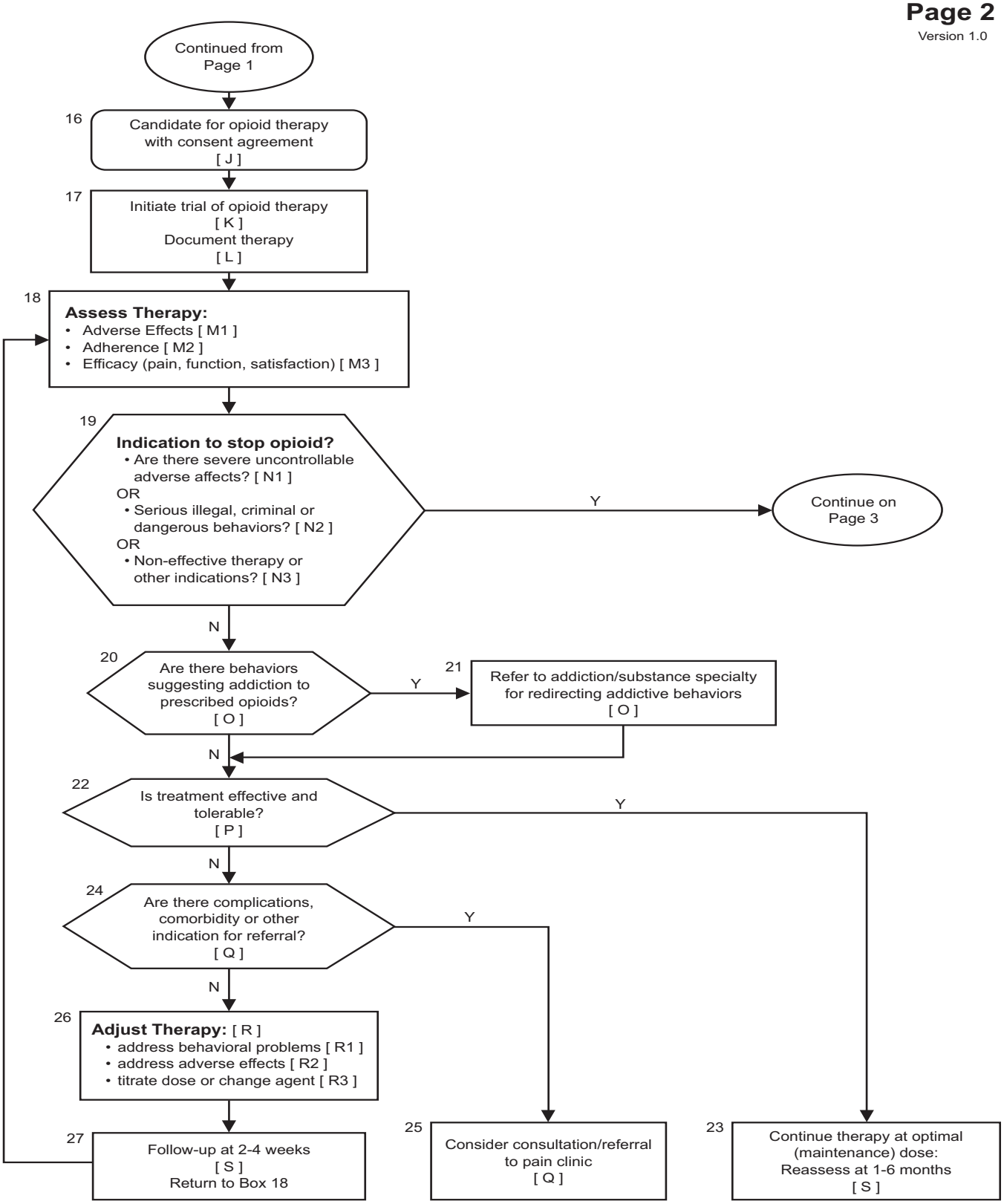

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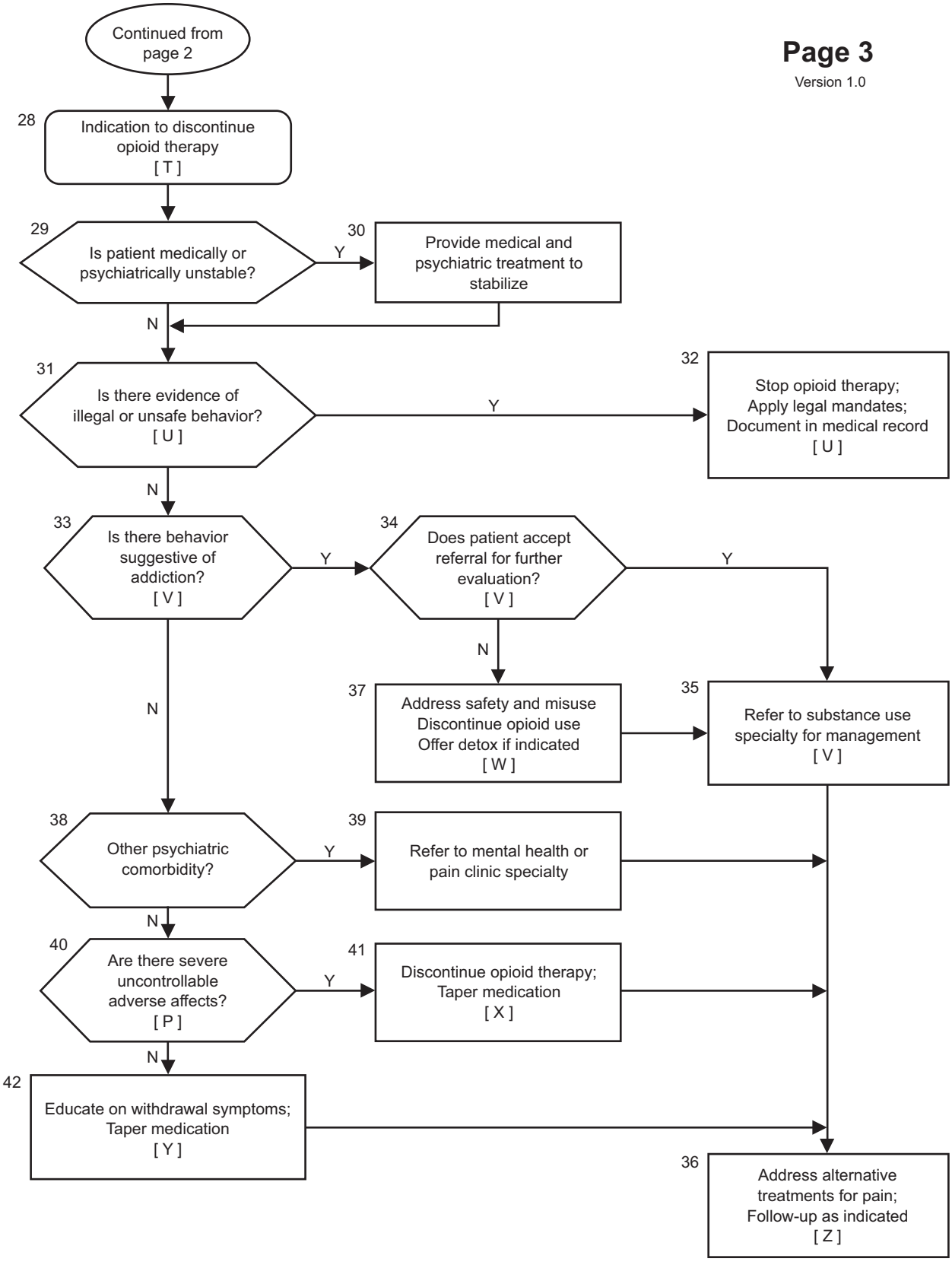


## ANNOTATIONS

### A. Patient with Chronic Non-Cancer Pain

The patient managed within this guideline suffers from chronic non-cancer pain. The patient has been previously assessed and treated, over a period of time, with non-opioid therapy or nonpharmacologic pain therapy. Because the response to treatment has not provided adequate pain relief, the patient is considered to be a candidate for a trial of opioid therapy.

In addition, because of the regulatory restrictions on the prescription of controlled substances, the guideline addresses the special considerations and documentation issues that are required for the safe and effective management of opioid therapy.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (IASP, 1994). The perception of pain is influenced by physiological, psychological, and social factors. The human reaction to the sensory experience of suffering takes on an added dimension in patients who have chronic non-cancer pain. Some of these patients may have, in addition to the persistent pain, overriding affective components and learned responses that can lead to severe psychological disability and a pattern of repeated interaction with the health care system.

### B. History and Physical Examination to Obtain Comprehensive Assessment

1. A comprehensive patient assessment should be completed to identify clinical conditions that may interfere with the appropriate and safe use of chronic opioid therapy.

   The comprehensive assessment should include:

   - Age, sex
   - History of present illness, including a complete pain assessment (see Annotation C)
   - Pain-related history (pain-related fear, pain interference with function, prior pain treatment)
   - Past medical and surgical history
   - Past psychiatric history (including depression, anxiety, other emotional disorders)
   - Substance use history
   - Family history
   - Social history (including employment, cultural background, social network, marital history, legal history, and other behavioral patterns, e.g., impulse behaviors)
   - Review of systems
   - Medications
   - Allergies
   - Physical examination
   - Mental Status Examination
   - Review of diagnostic studies and assessments
   - Evaluation of occupational risks and ability to perform duty

2. Information from the pain history and physical exam should be reviewed to ensure that the patient has had an adequate trial of non-opioid therapy.
3. Consider the use of a urine drug screen (UDS) or other laboratory tests to screen for the presence of illegal drugs, unreported prescribed medication, or unreported alcohol use.

### C. Complete Assessment of Pain; Determine Cause of Pain, If Possible

1. Pain intensity should be evaluated at each visit.
   - Intensity of pain should be measured using a numerical rating scale (0-10 scale) for each of the following:
     - Current pain
     - Least pain in last week
     - "Usual" or "average" pain in the last week
   - The patient's response to current pain treatments should be assessed at each visit using the following questions (some interventions may temporarily increase pain, so it may not always be appropriate to ask these questions):
     - "What is your intensity of pain after taking your current medication/using your current treatment?"
     - "How long does your pain relief last after taking your medication?"

- Other attributes of pain should be assessed as part of the comprehensive pain assessment:
  - Onset and duration
  - Location
  - Description (quality)
  - Aggravating and alleviating factors
  - Behavioral manifestations of pain
  - Impact of pain
  - Current and past treatments for pain
  - Patient's expectations for pain relief
- If possible, determine type of pain:
  - Differentiate between nociceptive and neuropathic pain
  - Consider further evaluation if needed (such as EMG or consultation)

2. Assessment of function should include:
   - Cognitive function (attention, memory, and concentration)
   - Employment
   - Enjoyment of life
   - Emotional distress (depression and anxiety)
   - Housework, chores, hobbies, etc.
   - Sleep
   - Mobility
   - Self-care behaviors
   - Sexual function
3. Information from the pain history and physical exam should be reviewed to ensure that the patient has had an adequate trial of non-opioid therapy.

**D. Are There Contraindications to Opioid Therapy That Cannot Be Resolved?**

1. Opioid therapy should not be used in the following situations (absolute contraindications):
   - Allergy to opioid agents (may be resolved by switching agents)
   - Co-administration of drug capable of inducing life-limiting drug-drug interaction
   - Active diversion of controlled substances (providing the medication to someone for whom it was not intended)
2. Opioid therapy should be used only after careful consideration of the risks and benefits (relative contraindications):
   - Acute psychiatric instability or high suicide risk
   - History of intolerance, serious adverse effects, or lack of efficacy of opioid therapy
   - Meets DSM-IV criteria for current substance use disorder (DSM IV, 1994)
   - Inability to manage opioid therapy responsibly (e.g., cognitively impaired)
   - Unwillingness or inability to comply with treatment plan
   - Unwillingness to adjust at-risk activities resulting in serious re-injury
   - Social instability
   - Patient with sleep apnea not on continuous positive airway pressure (CPAP)
   - Elderly patients
   - COPD patients
3. Consider consultation with an appropriate specialist if legal or clinical problems indicate that more intensive care related to opioid management is indicated. Patient with substance use problem should be referred to substance use specialty for concurrent treatment of substance use.

**E. Indications for Referral/Consultation**

1. The patient with complex pain conditions should be referred to a pain specialist for evaluation and treatment.
2. The patient with long-standing pain problems or multiple issues beyond pain alone should be referred to a multidisciplinary pain clinic for evaluation and treatment.
3. In the patient with a history of addiction or substance use disorder, or if drug screens are indicative of a drug or alcohol-use problem, consider consultation with an addiction specialist to evaluate the risk of recurrent substance abuse or to assist with ongoing management.

**F. Is Opioid Therapy Indicated at This Time?**

1. The use of opioid therapy is indicated for moderate to severe pain that has failed to adequately respond to other non-opioid therapeutic interventions.
2. The ethical imperative to relieve pain should be considered when evaluating therapeutic options.

**G. Educate Patient and Family about Treatment Options; Share Decision about Goal and Expected Outcome of Therapy**

1. The patient and family/caregiver should be involved in the educational process.
2. Written educational material should be provided in addition to discussion with patient and family/caregiver.
3. The opioid agreement should be discussed in detail (see Annotation H).
4. Patient education should be documented in the medical record.
5. The following topics should be included (see also Appendix B: Patient Education):
   - General information: goals and expectations, addiction, tolerance, physical dependency, withdrawal symptoms
   - Patient responsibilities: prescriptions, adherence to treatment plan, obtaining medications from a single source, pain diary, feedback to the provider
   - Legal issues
   - Instruction on how to take medication: importance of dosing and timing, interaction with other drugs
   - Prophylactic treatment of adverse effects and management of constipation

**H. Obtain a Treatment Agreement**

1. A patient consent in the form of a *written treatment agreement* should be obtained before initiating opioid therapy. The patient's responsibilities during therapy should be discussed with patient and family, addressing the following issues (for a sample agreement, see Appendix C):
   - Goals of therapy: partial relief and improvement in physical, emotional, and/or social functioning
   - The requirement for a single provider or treatment team
   - The limitation on dose and number of prescribed medications and the proscription against changing dosage without permission; discuss the use of "pill counts"
   - A prohibition on use with alcohol, other sedating medications, or illegal medications without discussing with provider
   - Agreement not to drive or operate heavy machinery until medication-related drowsiness is cleared
   - Responsibility to keep medication safe and secure
   - Prohibition of selling, lending, sharing, or giving any medication to others
   - Limitation on refills: only by appointment, in person, and no extra refills for running out early
   - Compliance with all components of overall treatment plan (including consultations and referrals)
   - The role of urine drug screening and alcohol testing
   - Acknowledgement of adverse effects and safety issues such as the risk of dependence and addictive behaviors
   - The option of sharing information with family members and other providers, as necessary
   - Need for periodic reevaluation of treatment
   - Consequences of nonadherence

**I. Determine and Document Treatment Plan**

1. The treatment plan should be individually tailored to the patient's circumstances and to the characteristics of the patient's pain.
2. Consider the use of other treatment approaches (supervised therapeutic exercise, biofeedback, and cognitive behavior approaches), which should be coordinated with the opioid therapy.
3. Consider establishing a referral and interdisciplinary team approach, if indicated.
4. Establish a follow-up schedule to monitor the treatment and patient progress.
5. The treatment plan and patient preferences should be documented in the medical record.

**J. Candidate for Opioid Therapy, with Consent**

Opioid therapy can be initiated in the form of a therapeutic trial. Prior to such a trial, the patient should be fully informed and should consent to the therapy. As treatment is administered, close monitoring of outcomes (pain relief, adverse effects, physical and psychosocial functioning, or any aberrant drug-related behaviors), along with careful titration, can establish successful long-term therapy.

## DEFINITIONS

### Physical dependence

Physical dependence on an opioid is a physiologic state in which abrupt cessation of the opioid, rapid tapering (e.g., when a patient forgets to take the medication), or administration of an opioid antagonist results in a withdrawal syndrome. Physical dependency on opioids is an expected occurrence in all individuals in the presence of continuous use of opioids for therapeutic or for nontherapeutic purposes. It does not, in and of itself, imply addiction (ASAM, 1997).

### Tolerance

Tolerance is a form of neuroadaptation to the effects of chronically administered opioids (or other medications), which is manifested by the need for increasing or more frequent doses of the medication to achieve the initial effects of the drug. Tolerance may occur both to the analgesic effects of opioids and to some of the unwanted adverse effects, such as respiratory depression, sedation, and nausea. The appearance of tolerance is variable in occurrence, but it does not, in and of itself, imply addiction (ASAM, 1997).

### Addiction

Addiction in the context of pain treatment with opioids is characterized by a persistent pattern of dysfunctional opioid use that may involve any or all of the following:

- Loss of control over the use of opioids
- Preoccupation with obtaining opioids, despite the presence of adequate analgesia
- Continued use despite physical, psychological, or social *adverse consequences* (ASAM, 1997).

### Pseudoaddiction

Pseudoaddiction describes patient behaviors that may occur when pain is under treated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. In contrast to true addiction, in pseudoaddiction the behaviors resolve when the pain is effectively treated (ASAM, 1997). Misunderstanding of this phenomenon may lead the clinician to inappropriately stigmatize the patient with the label "addict." In the setting of unrelieved pain, the request for increases in drug dose requires careful assessment, renewed efforts to manage pain, and avoidance of stigmatizing labels.

## K. Initiate Trial of Opioid Therapy

### Initiation Phase

**Objective:** To find the medication(s) that provide(s) the best pain relief with the fewest adverse effects at the lowest effective dose.

Effective therapy is achieved when the patient reports improvement in pain relief and/or function along with minimal or acceptable adverse effects.

The general strategy for the initiation phase:

1. For intermittent pain, begin with short-acting opioids (such as morphine, oxycodone, or hydrocodone), trying one medication at a time.
2. For continuous pain, an agent with a long duration of action, such as controlled-release (CR) morphine or methadone, is recommended.
3. A trial should be considered for either nociceptive or neuropathic pain. Neuropathic pain often requires higher doses of medication than nociceptive pain.
4. Begin with a low test-dose to make sure that the medication has no serious or intolerable adverse effects. Administration by the least invasive route is recommended; oral administration is preferred.
5. For patients with specific medical conditions, choice of agent will depend on route and special cautions. Preferred choices are suggested in Table 1, Use of Opioids for Chronic Pain in Special Populations.
6. In opioid-naïve patients, one medication should be tried at a time, with frequent evaluations to titrate the dose. Patients with prior experience with opioid medications for pain relief should use the medication that worked well in the past, at the dose to which the patient was accustomed.
7. Education that addresses anticipated adverse effects, the use of medication, and symptoms of opioid withdrawal should be provided to the patient and family.

8. Constipation, which is anticipated with all opioids, should be treated prophylactically.
9. Failure to show partial analgesia with incremental dose titration may be evidence for pain that is not opioid-responsive, and suggests that the opioid therapy should be discontinued.

**Titration Phase**

**Objective:** To adjust the dose of opioid to achieve satisfactory pain relief and tolerable adverse effect profile.

Once a medication has been found that provides pain relief, it is likely to continue to provide pain relief, as long as the dose is increased to compensate for analgesic tolerance, if it develops.

Opioids almost always need to be titrated upwards, and effective doses are commonly higher than the starting dose. The eventual dose must be one at which the clinician can comfortably maintain the patient. Personal discomfort by the clinician at the apparent level of opioid requirement is a valid reason not to proceed, and may warrant the referral of the patient to a physician who has more expertise in chronic pain management.

The general strategy for the titration phase:

10. Once a pain relief response has been achieved at a particular dose, repeat that dose as the level of pain begins to rise; this approach helps establish the dosing interval.
11. If necessary, the initial daily dose may be increased by 25% to 100%. If the new dose is well tolerated but ineffective, additional increases in dose can be considered. See R3 for dosage titration recommendations.
12. As the patient develops tolerance, adverse effects noted during the initial period of exposure to a medication are likely to disappear.
13. If a medication provides less than satisfactory pain relief or uncontrollable adverse effects, consider rotating to an alternate opioid medication.
14. In general, there is no pharmacological rationale for using a predetermined maximal dose for pure agonist opioids. Long-term opioid therapy should be started at a low dose and carefully titrated until an adequate level of analgesia is obtained, or until unmanageable and persistent adverse effects warrant a decreased dose or a change in therapy. For some patients, however, opioids do not exert an appreciable analgesic effect until a threshold dose has been achieved.
15. If short-acting medications are effective and well tolerated, it may be possible to achieve equivalent pain relief with fewer daily doses of medication by substituting an equivalent dose of long-acting opioid medication (such as methadone, morphine CR, or oxycodone CR). These long-acting medications may provide steadier serum levels and smoother pain control and can be supplemented with doses of short-acting medication to control pain exacerbation.
16. During the titration phase, reasonable doses of rescue opioid may be provided and can be used to assess the adequacy of the overall opioid dose (see Appendix E, Table E5).
17. The conversion to a long-acting opioid should be based on an equianalgesic conversion (see Appendix E, Table E3, for conversion factors) and consideration of the incomplete cross-tolerance between opioids. To allow for incomplete cross-tolerance, in most cases the starting conversion dose should be 50% to 67% of the calculated equianalgesic dose.
18. Precise record-keeping of the time and dose of medication, the degree of pain relief, and the occurrence of adverse effects is essential for successful titration. Maintaining close communication with patients and families and explicitly laying out the criteria for evaluating the effects of analgesic medications can help in defusing the anxiety that often accompanies visits to the physician.

**Maintenance Phase**

**Objective:** To maintain reliable pain control and improvement in function by repeating the effective dose in a routine schedule, varying the timing or dose only to accommodate changes in activity level or exacerbations of pain.

The general strategy for the maintenance phase:

19. The dose should not be lowered once a plateau has been achieved that provides adequate pain relief and satisfactory functional status and is tolerated.
20. To ensure patient safety, continue routine patient reporting and monitoring. Patients should be asked

to report not only on their medical conditions and medication requirements, but also any changes in their activity, employment, or social situation.

21. When prescribing an opioid analgesic for around-the-clock pain, it should also be dosed around the clock using a pharmacologically appropriate, time-contingent, dosing schedule.
22. In addition to the maintenance opioid analgesic, supplemental doses of short-acting medications may be considered to control breakthrough occasional episodes of pain exacerbation, such as those listed below (also see Appendix E, Table E5).
    a. Incidental pain: pain related to an increase in activity
    b. End-of-dose pain
    c. Natural conditions: pain related to predictable phenomena, such as changes in the weather
    d. Specific medical conditions

    Higher doses of the long-acting maintenance medication may also be useful in certain situations, but the potential for drug accumulation and adverse effects should be considered. If episodes of pain exacerbation occur frequently, reevaluation of the adequacy of the maintenance dosage regimen is warranted.
23. Patients need to be assessed every 1 to 6 months, keeping the following in mind:
    a. No specific visit frequency applies to all patients.
    b. The visit frequency should be adjusted based on patient characteristics, comorbidities, type of pain, and type and dose of opioids. The provider should select a frequency that allows close follow-up of the patient's adverse effects, pain status, and appropriate use of medication.
    c. The patient should be able to request an early evaluation.
    d. In general, any change of dose or drug should be done during a clinic visit.

## Table 1: Use of Opioids for Chronic Pain in Special Populations

| Medication | Swallowing Difficulty | GI Malabsorption | Elderly or Debilitated | Hepatic Dysfunction | Renal Dysfunction | Seizures | Decreased CYP-2D6 Activity [c] |
|---|---|---|---|---|---|---|---|
| Codeine | ✚ (OS) | | ◆ and ↓ | ✖ | ◆ and ↓ | | Less effective |
| Fentanyl TDS[a] | ✚ | ✚ | | ◆ and ↓ | | | |
| Hydrocodone | ✚ (OS) | | | | | | ? less effective |
| Hydromorphone | ✚ (OS, RS) | ✚ (RS) | | | | | |
| Levorphanol | | | | | | | |
| Methadone[b] | ✚ (OS) | | | | | | |
| Morphine | ✚ (OS, RS) | ✚ (RS) | | | ↓ or ✖ | | |
| Morphine CR/SR | | | | | ↓ or ✖ | | |
| Oxycodone | ✚ (OS) | | | | ◆ and ↓ | | ? less effective |
| Oxycodone CR | | | | | ◆ and ↓ | | ? less effective |
| Propoxyphene | | | ✖ | ✖ | ✖ | ◆ | |
| Tramadol | | | ◆ and ↓ | ◆ and ↓ | ◆ and ↓ | ✖ | ? less effective |

See Appendix E, Tables E1 and E2, and Appendix F for further details and references

CR = Controlled release
OS = Oral solution
RS = Rectal suppository
SR = Sustained release
TDS = Transdermal system

✚ = Recommended
◆ = Use with caution
↓ = Reduce dose
✖ = Not recommended
? Less effective = conversion to the active metabolite may be decreased. Impact on analgesic efficacy is unknown.

[a] Transdermal System, consider if oral intake or bowel absorption is impaired.

[b] The only long-acting opioid available as an oral solution.

[c] **CYP-2D6 Inhibiting Drugs:** *Antiarrhythmics* (amiodarone, propafenone, quinidine [strong inhibitor]); *analgesics* (methadone [weak inhibitor], propoxyphene); *antihistamines* (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); *histamine$_2$ receptor antagonists* (cimetidine); *neuroleptics* (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); *protease inhibitors* (ritonavir), *quinine compounds* (hydroxychloroquine, quinacrine, quinine); *selective serotonin reuptake inhibitors* (fluoxetine, fluvoxamine, paroxetine, sertraline), and *miscellaneous compounds* (clomipramine, ketoconazole, ticlopidine).

## L. Document Therapy

1. When writing a prescription for opioid therapy, be certain to record the name of the drug, the strength, the number of dosage units (written numerically and in text), and how the drug is to be taken. Record any changes to therapy and the reason for the changes. For methadone, indicate on the prescription that it is for chronic pain.
2. The VA regulations for the use of controlled substances (Controlled Substances [Pharmacy Stock], VHA Handbook 1108.1) must be followed by clinicians within the VA system, and provide a useful guide for other clinicians.
   - All prescriptions for controlled substances will be dated as of and signed on the day when issued and bear the full name and address of the patient, and the name, address, and Drug Enforcement Agency (DEA) registration number of the practitioner. Prescriptions should not be filled if they are more than 7 days old when presented.
   - An intern, resident, mid-level practitioner, foreign-trained physician, physician, or dentist on the staff of a VA facility exempted from registration (21 CFR 1301.24) will include on all prescriptions issued the registration number of the VA facility and the special internal code number assigned by the VA facility in lieu of the registration number of the practitioner required by law (21 CFR 1306.05b). Each written prescription will have the name of the physician or authorized practitioner stamped, typed, or hand-printed on it, as well as the signature of the physician or authorized practitioner.
   - The label of any drug listed as a "Controlled Substance" in Schedule II, III, IV, or V of the Controlled Substances Act will, when dispensed to or for a patient, contain the following warning: "CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed."

## M. Assess Therapy

### M1. Assess Adverse Effects

1. Evaluate patient for opioid adverse effects: constipation, nausea, vomiting, headache, dyspepsia, pruritus, dizziness, tiredness, dry mouth, sweating, hyperalgesia, sexual dysfunction, and sedation.
2. Many adverse effects spontaneously resolve with continued administration and development of tolerance. Consider individual levels of tolerability to different opioid agents.
3. If not already done, anticipate and consider preventive treatment for common adverse effects, particularly constipation and nausea.
4. Modifying the dose and rotating the opioid agents should successfully treat most adverse effects.

### M2. Assess Adherence

1. At every visit, assess and document adherence with appropriate use of opioid analgesics, including evidence of misuse, abuse, or addiction. (Consider random pill counts or urine drug screens to assess adherence).
2. Assess and document adherence to other components of the treatment plan, such as follow-up with referrals, tests, and therapies.
3. Assess and document patient motivation and barriers to adherence.
4. Assess patients for behaviors that are predictive of addiction.
5. If the meaning of the behavior is not clear, some time may be required to assess the patient correctly and observe the reaction to additional requirements, such as frequent clinic visits or periodic drug screens.

| Table 2: Predictors of Opioid Misuse | |
|---|---|
| **I** | **Illegal or Criminal Behavior** |
| | • Diversion (sale or provision of opioids to others)<br>• Prescription forgery<br>• Stealing or “borrowing” drugs from others |
| **II** | **Dangerous Behavior** |
| | • Motor vehicle crash /arrest related to opioid or illicit drug or alcohol intoxication or effects<br>• Intentional overdose or suicide attempt<br>• Aggressive/threatening/belligerent behavior in the clinic |
| **III** | **Behavior that Suggests Addiction** |
| | • Use of prescription medications in an unapproved or inappropriate manner (such as cutting time-release preparations, injecting oral formulations, and applying fentanyl topical patches to oral or rectal mucosa)<br>• Obtaining opioids outside of medical settings<br>• Concurrent abuse of alcohol or illicit drugs<br>• Repeated requests for dose increases or early refills, despite the presence of adequate analgesia<br>• Multiple episodes of prescription “loss”<br>• Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber, or after warnings to desist<br>• Evidence of deterioration in the ability to function at work, in the family, or socially, which appears to be related to drug use<br>• Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug<br>• Positive urine drug screen—other substance use |
| **IV** | **Aberrant Behavior that Requires Attention** |
| | • Aggressive complaining about needing more of the drug<br>• Drug hoarding during periods of reduced symptoms<br>• Requesting specific drugs<br>• Openly acquiring similar drugs from other medical sources<br>• Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions<br>• Unapproved use of the drug to treat another symptom<br>• Reporting psychic effects not intended by the clinician<br>• Resistance to a change in therapy associated with “tolerable” adverse effects, with expressions of anxiety related to the return of severe symptoms<br>• Missing appointment(s)<br>• Not following other components of the treatment plan (physical therapy, exercise, etc.) |

## M3. Assess Efficacy (Pain, Function, and Satisfaction)

1. The provider should evaluate pain intensity at each visit.
   - Intensity of pain should be measured in the following manner using a numerical rating scale (NRS) (0-10):
     - Current pain
     - Least pain in last week
     - "Usual" or "Average" pain in the last week
   - The patient's response to current pain medications should be assessed each visit using the following questions:
     - "What is your intensity of pain after taking your current medication/treatment?"
     - "How long does your pain relief last after taking your medication?"
2. Providers should evaluate pain-related function using validated instruments or numerical rating scales on a monthly basis during titration and every six months after the patient is on stable opioids. Assessment of function should include:
   - Employment
   - Enjoyment of life
   - Emotional distress (depression and anxiety)
   - Housework, chores, hobbies, etc.
   - Sleep
   - Mobility
   - Self-care behaviors
   - Sexual function
3. The patient's satisfaction with pain control should be assessed at each visit.

## N. Indication to Stop Opioid Therapy

## N1. Are There Severe and Uncontrollable Adverse Effects?

1. When therapy is a greater detriment than benefit, as determined in consultation with the patient and family, opioid therapy should be discontinued.

## N2. Serious Nonadherence: Illegal, Criminal, or Dangerous Behaviors?

1. Address safety issues immediately. Apply legal mandates as appropriate.
2. Dangerous or illegal behaviors may require immediate cessation of the opioid therapy with appropriate treatment of potential withdrawal symptoms.
3. Consider notifying police about criminal behaviors. Consult with counsel prior to doing so to clarify current confidentiality laws and regulations.

## N3. Noneffective Therapy or Other Indications to Stop Therapy?

1. Consider tapering off opioid medication if the patient claims or exhibits:
   - Lack of efficacy
     - Continuing pain despite titration of dose to intolerable adverse effects
     - Lack of response despite trials of several different kinds of opioids
     - Decrease in overall function
   - Resolution of the pain problem
     - Pain problem may be resolved due to surgical intervention
     - Pain problem may be resolved due to physical therapy or other modalities
     - Pain may now be responding to non-opioid medications
   - Desire to discontinue therapy
     - Patient desires to stop opioid due to personal goals or interference with lifestyle, work, or quality of life
     - Patient desires to change to non-opioid therapy
     - Patient had been using opioids to enable other therapy which is now completed

## O. Is There Evidence of Nonadherence or Medication Misuse Suggestive of Addiction to Prescribed Opioid?

1. Screen for substance use disorders in patients who are unable or unwilling to adhere to the treatment plan.
2. Document and refer to addiction specialists those patients demonstrating behaviors suggesting addiction to prescribed opioids or substance use disorders.
3. Consider referring patients with significant, chronic, substantiated pain who develop addiction behaviors in the context of chronic opioid therapy. An addiction specialist may be better able to evaluate the risks and benefits of continuing opioid therapy in such a situation.

## P. Is Treatment Effective and Tolerable?

1. Assess the safety and efficacy of the opioid trial, using the following criteria:
   - Patient's report of pain intensity and/or functional status
   - Persistence of analgesia between doses (i.e., pain relief is of adequate duration)
   - Patient satisfaction with the level of pain relief
   - Patient's improvement in functional status, quality of life
   - Patient's ability to participate in other modalities such as physical therapy
   - Patient's tolerance and management of adverse effects
2. Emphasis should be given to capitalizing on improved analgesia by gains in physical and social function; opioid therapy should be considered complementary to other analgesic and rehabilitative approaches.

## Q. Are There Complications, Comorbidities, or Other Indications for Referral?

1. Referral to a specialist in pain medicine may be warranted, depending on the expertise of the provider and the complexity of the problem.
2. Referral to a psychiatrist or psychologist may be indicated in cases of significant psychiatric comorbidity.
3. Patients with other psychosocial problems or comorbidities may benefit from disease or case management.

## R. Adjust Therapy

### R1. Address Minor Nonadherence or Medication Misuse

1. Consider adjustment of the initial treatment agreement, with emphasis upon specific adherence issues that have been identified; a more rigid approach may be required.

   Possible responses to medication misuse might include:
   - Education and discussion along with restatement of the opioid management plan or agreement
   - Reviewing the written opioid prescribing agreement
   - Recommending or insisting on consultation with a pain and/or addiction specialist
   - Discussion, including discussion with others involved in the patient's care
   - Administration of medications under supervision or with the assistance of others
   - Change of medication or amount dispensed
   - More frequent clinic contacts (telephonic, physician extenders, or clinic visits)
   - Instituting regular or random urine toxicology screens as a condition for prescription renewal
2. Consider consultation with or referral to mental health if exacerbation of an underlying psychotic disorder is an issue.
3. Consider setting up a grievance procedure with the patient.
4. Consider whether the patient requires a living situation with greater structure (e.g., nursing home, assisted living facility)
5. Strongly consider involving the patient's family or significant others in finding solutions to nonadherence, as well as monitoring future adherence.

### R2. Address Adverse Effects

Adverse effects can be minimized through the use of preventive therapy or by switching to a different opioid:

1. A general strategy to minimize adverse effects is modifying the dose of medication during titration or rotating the opioid agent.

2. The following adverse effects are the most common. A prophylactic treatment and specific patient education should be provided together with initiation of therapy. Symptomatic treatment should be augmented with dose modification and/or opioid rotation.

   a. **Constipation** - Provide prophylactic treatment for the predictably constipating effects of opioid therapy. Constipation can be managed with a stepwise approach that includes an increase in fiber and fluids, osmotic agents (e.g., sarbitol or lactulose), or with a combination stool softener and a mild peristaltic stimulant laxative, such as senna or bisacodyl, as needed (Sykes, 1996a; Passik and Weinreb, 2000).

   b. **Nausea and vomiting** - Consider prophylactic antiemetic therapy.

   c. **Itching** - Rule out an allergic reaction; consider treatment with antihistamines.

3. Opioids may cause adverse behavioral or cognitive effects. Evaluation and treatment may be indicated and consultation or referral to a mental health specialist may be considered. Specific attention should be given to other non-opioid medications that the patient is using.

   a. **Cognitive adverse effects** - Sedation, confusion, and deterioration of cognitive function can be managed effectively using such measures as dosage reduction (with or without co-analgesia); change of opioid agent; addition of psychostimulant; elimination of other drugs or conditions that may contribute to adverse effects (Passik and Weinreb, 2000).

   Concurrent sedative use may cause cognitive deficits in patients on chronic opioid therapy (Canadian Pain Society, 1998). Cognitive deficits may worsen on opioid therapy; therefore caution is advised.

   b. **Perceptual or affective adverse effects** (hallucinations, depression)

   Evaluation of hallucinations is often performed by trial-and-error techniques. All nonessential CNS-acting medications (e.g., steroids) should be eliminated.

4. Sexual dysfunction

   Hormone balance may be affected by opioids. Further evaluation and consultation should be considered.

5. The following adverse effects are best treated by dose reduction during titration or opioid rotation:
   - Sweating
   - Peripheral edema
   - Urinary retention
   - Myoclonus
   - Hyperalgesia
   - Dyspepsia

## R3. Titrate Dosage or Change Agent to Achieve Stable Pain Relief

1. Documentation is essential and should demonstrate the evaluation process—including consultation, prescriptions, and periodic review of patient status.
2. Consider one or more of the following adjustments in therapy:
   - Increase dose titration. Increase dose by 25% to 100%. An increase of less than 25% is not appropriate.
   - To ensure that the full effect from a dosage change has been manifest and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every 5 half-lives.
   - If possible, titrate only one drug at a time, while observing the patient for additive effects. Inappropriate medications should be tapered while initiating an appropriate pharmacologic regimen.
   - Medication may be increased until limited by adverse effects or clear evidence of lack of efficacy.
   - Rotate to another agent based on equianalgesic table and titrate as indicated above.
   - Provide a drug holiday.
   - In some patients receiving long-term opioid therapy, rotation between opioids may help to improve efficacy and reduce dose escalation.
3. For a patient with continuous pain, an agent with a long duration of action, such as controlled-release morphine or methadone, is recommended.
4. Maintain patients on as few medications as possible. Drug interactions and adverse events increase as the number of medications in a regimen increases. Discontinue medications, especially adjuvant medications, which do not add substantially to patient function or comfort.

## S. Follow Up at Appropriate Intervals

1. At each visit, assessment should address:
   - Comfort (degree of analgesia)
   - Opioid-related side-effects
   - Functional status (physical and psychosocial)
   - Adherence to opioid therapy contract and other aspects of treatment plan
2. Use of self-report instruments (diary, opioid log) may be helpful but should not be required.
3. Documentation is essential, and the medical record for each encounter should specifically address comfort, function, adverse effects, and treatment plan adherence.
4. Visits should be scheduled at least every 2 to 4 weeks for the first 1 to 2 months of the trial (titration phase), and then at least once every 1 to 6 months for the duration of the therapy (maintenance).
5. A consultation should be requested if:
   - The patient requires doses of opioids beyond what is usually required for his/her condition or beyond what the provider is comfortable prescribing.
   - Pain and functional status have not substantially improved after 3 months of opioid treatment.
   - A patient has a new or recurrent substance use disorder, or is at high risk for relapse to a substance use disorder (substance use disorder specialist consultation).
   - A patient appears to have significant problems with depression, anxiety, or irritability (a psychiatric consultation may be indicated in such cases).
6. Laboratory studies (especially liver or kidney function screens) and/or drug screens should be ordered as indicated.

## T. Indication to Discontinue Opioid Therapy

At this point the clinician will have reached the decision to discontinue opioid therapy for one of the following reasons: (1) uncontrolled adverse effects; (2) serious nonadherence to the treatment plan or unsafe behaviors; (3) lack of effectiveness of therapy or a desire on the part of the patient to discontinue therapy.

## U. Is There Evidence of Illegal or Unsafe Behavior? Stop Opioid Therapy; Apply Legal Mandates; Document in Medical Record

1. Opioid therapy should be discontinued immediately in the following cases:

**Table 2a: Predictors of Opioid Misuse**

| Illegal or Criminal behavior |
|---|
| • Diversion (sale or provision of opioids to others)<br>• Prescription forgery<br>• Stealing or "borrowing" drugs from others |
| **Dangerous behavior** |
| • Motor vehicle crash/arrest related to opioid or illicit drug or alcohol intoxication or effects<br>• Intentional overdose or suicide attempt<br>• Aggressive/threatening/belligerent behavior in the clinic |

2. Consider notifying law enforcement authorities about patients who are suspected of prescription fraud or diversion (e.g., VA police, risk manager, and/or regional counsel).
3. Carefully document the details of the situation.
4. Document and refer to mental health specialists those patients demonstrating behaviors suggestive of suicide.

## V. Addiction Behavior: Refer to Substance Use Disorder Specialist

1. Patients manifesting behaviors characteristic of compulsive drug use (addiction) to either opioids or other drugs or alcohol should be referred to a substance use disorder specialist. If there are clearly unsafe or illegal behaviors, opioid prescribing should stop immediately and withdrawal addressed.
2. In other circumstances, a decision might be made to either taper and discontinue opioid prescribing, or wait until after consultation has been obtained.
3. If opioid agonist therapy for opioid addiction (e.g., methadone maintenance) is being considered, it may be helpful to wait to taper the prescribed opioids until the diagnosis is clarified and opioid agonist therapy induction begun.

4. Patients with complex conditions with multiple comorbidities, including other psychiatric disorders, should be referred to an addiction medicine or addiction psychiatry specialist for the management of opioid discontinuation.

## W. Address Safety and Misuse; Begin Process to Discontinue Opioid Use

1. Maintain contact with any patient who withdraws from treatment due to a disagreement.
2. Refer patients with comorbid psychiatric disorders to appropriate mental health providers.

## X. Discontinue Opioid Therapy; Taper Medications

1. Opioid detoxification in a primary care setting followed by ongoing substance use treatment may be appropriate for selected opioid-dependent patients.
2. Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.

## Y. Educate on Withdrawal Symptoms; Taper Medications

1. Complete evaluation of treatment, comorbidity, psychological condition, and other relevant factors should be completed prior to the initiation of the taper.
2. Clear written instructions should be given to patients/family to educate them about the slow taper protocol that will minimize abstinence (withdrawal) syndromes.
3. Patients who are unable to tolerate the taper as described should be considered for referral to or consultation with a pain specialist, substance use specialist, or other expert.
4. Detoxification for addicted patients is not part of this guideline. Refer to the VA/DoD Guideline for the Management of Substance Use Disorders.

**Protocol for Tapering:**

- Taper by 20% to 50% per week [of original dose] for patients who are not addicted. The goal is to minimize adverse/withdrawal effects.
- The rapid detoxification literature indicates that a patient needs 20% of the previous day's dose to prevent withdrawal symptoms.
- Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.
- Some experts suggest that the longer the person has been on opioids, the slower the taper should be.
- Remain engaged with the patient through the tapering process, and provide psychosocial support as needed.

## Z. Follow Up as Indicated

RECOMMENDATIONS

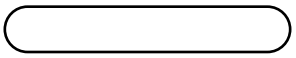
1. Do not abandon a patient under any circumstances.
2. Maintain contact with any patient who withdraws from treatment due to a disagreement.
3. Refer patients with comorbid psychiatric disorders to appropriate mental health providers.
4. Discontinue opioid therapy using a safe tapering protocol.

**Table 4: Grade the Recommendation**

| | |
|---|---|
| **A** | A strong recommendation that the intervention is always indicated and acceptable |
| **B** | A recommendation that the intervention may be useful/effective |
| **C** | A recommendation that the intervention may be considered |
| **D** | A recommendation that a procedure may be considered not useful/effective, or may be harmful |
| **I** | Insufficient evidence to recommend for or against – the clinician will use clinical judgment |

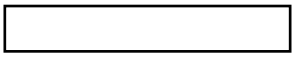
# APPENDIX A

## KEY TO ALGORITHM



Rounded rectangles represent a clinical state or condition.

Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.



Rectangles represent an action in the process of care.

Ovals represent a link to another section within the guideline.

# APPENDIX B

## PATIENT EDUCATION

**Patient/family/caregiver education**

- Involve the family, guardian, or other caregivers in the educational process.
- Provide appropriate written educational materials to patients and caregivers.
- Discuss the opioid agreement.
- Document all patient education activities in patients' medical records.

**Topics to be included in patient education**

**General information**

- Explain that the purpose of long-term opioid therapy is to improve functional status and alleviate, rather than eliminate, pain.
- Establish realistic and specific functional goals and expectations that can be assessed to evaluate the success of therapy.
- Review the process of the opioid trial, titration, and maintenance stages, and discuss expected responses such as opioid responsiveness, tolerance, and physical dependency.
- Explain the monitoring process and discuss the criteria to stop therapy if chronic opioid therapy (COT) is no longer indicated as the preferred treatment for pain. These criteria include: (1) the treatment is not effective; (2) patients experience serious adverse effects; (3) there is a decrease in function; or (4) patients are unable to adhere to the treatment plan.
- Explain the importance of patient self-reporting and feedback in monitoring the effectiveness of treatment and the management of adverse effects.
- Review the procedure for patients to follow if a problem related to opioid therapy (emergency situation) occurs outside your regular office hours.
- If therapy is to be discontinued, explain the process of tapering the medications in a controlled fashion and discuss withdrawal symptoms and how to manage them.
- If a patient is pregnant, advise that opioid therapy use may adversely affect the fetus.
- If a patient is breastfeeding, advise that COT use may adversely affect the breastfeeding child.

**Medication**

- Emphasize the importance of keeping the medication in a safe and secure place.
- Provide instruction on the use of the medication, including dosage, route, and timing.
- Explain the importance of adherence to dosing instructions.
- Provide advice on potential drug interactions with opioids.
- Advise that drowsiness is a common adverse effect during titration, and patients should not drive or operate heavy machinery until drowsiness is cleared.
- Review common adverse effects of opioid medications and how to manage them (prophylactic treatment).

**Patient responsibilities**

Adherence to treatment plan

- Inform patients that opioids are part of a total treatment plan. Inform patients that they are expected to participate fully in the treatment and to follow advice regarding physical therapy, psychotherapy, vocational rehabilitation, counseling, other medication, and other prescribed or recommended treatment.
- Inform patients that adherence to the treatment plan and dosage regimen, consultations, assessments, and adjunctive treatments is required. Patients should communicate any questions or concerns, such as adverse effects or dosing questions, to provider or nurse.
- Discuss patient and caregiver responsibilities for reporting pain and adherence, and explain patients' responsibilities for providing feedback, possibly in the form of a pain diary.

Obtaining prescriptions and refill policy

- Advise patients to obtain medications from the same provider or designee and the same pharmacy, and inform them that they are expected to fill medication prescriptions on time during a scheduled clinic appointment. They should not get their medications filled in an emergency room. Prescriptions cannot be filled early.
- Patients should inform any hospital or emergency room doctors that they receive pain medications from your office. Tell patients to ask their dentist to contact your office before giving any medications.
- Notify patients to contact their physician before taking other medications such as sedatives, muscle relaxants, other pain medications, or allergy and cold medications. Advise patients to avoid the use of alcohol, cocaine, marijuana, or other illegal drugs.

Safety

- Advise patients not to drive or operate heavy machinery if they feel tired, mentally foggy or are experiencing other adverse effects from the medications. It is patients' responsibility to keep themselves and others from harm.

The opioid agreement

- Notify patients that random urine drug screens may be required.
- Explain the consequences of nonadherence to the agreement.

**Legal issues**

- Review regulatory issues with patients and make it clear that it is illegal to give away, trade, share, or sell opioids to anyone other than the person being prescribed therapy.
- Review the potential impact of regulatory issues on occupation, lifestyle, and use (e.g., pilots, commercial drivers).
- Remind patients that they should keep COT medications in a secure place. Patients must immediately report stolen medications both to the police and to your office.

**Patient concerns**

- Address concerns and misconceptions, such as the risk of addiction and possible stigma associated with opioid therapy.
- Review the differences between tolerance, physical dependence, and addiction.
- Explain and describe withdrawal symptoms and how to manage them.
- Answer any other questions patients or family may have regarding the therapy.

# APPENDIX C

## AGREEMENT SAMPLE

1. I understand that my provider and I will work together to find the most appropriate treatment for my chronic pain. I understand the goals of treatment are not to completely eliminate pain but to partially relieve my pain in order to improve my ability to function. Chronic opioid therapy is only ONE part of my overall pain management plan.
2. I understand that my provider and I will continually evaluate the effect of opioids on achieving the treatment goals and make changes as needed. I agree to take the medication at the **dose** and **frequency prescribed** by my provider. I agree not to increase the dose of opioids on my own and understand that doing so may lead to the treatment with opioids being stopped.
3. I understand that the common adverse effects of opioid therapy include constipation, nausea, sweating and itchiness of the skin. Drowsiness may occur when starting opioid therapy or when increasing the dosage. I agree to refrain from driving a motor vehicle or operating dangerous machinery until such drowsiness disappears.
4. I will not seek opioid medications from another physician. Regular follow-up care is required, and only my provider will prescribe these medications for me at scheduled appointments.
5. I will attend all appointments, treatments and consultations as requested by my providers. I will attend all pain appointments and follow pain management recommendations.
6. I will not give or sell my medication to anyone else, including family members; nor will I accept any opioid medication from anyone else. I agree to be responsible for the secure storage of my medication at all times. If these medications are stolen, I will report this to police and my provider and will produce a police report of this event.
7. I understand that if my prescription runs out early for any reason (for example, if I lose the medication or take more than prescribed), my provider will not prescribe extra medication for me. I will have to wait until the next prescription is due.
8. I understand that the use of other medications can cause adverse effects or interfere with opioid therapy. Therefore, I agree to notify my provider of the use of all substances, including marijuana, alcohol, tranquilizers, and all illicit drugs.
9. I agree to periodic unscheduled drug screens.
10. I understand that I may become dependent on opioid medications, which in a small number of patients may lead to addiction. I agree that if necessary, I will permit referral to addiction specialists as a condition of my treatment plan.
11. I understand that my failure to meet these requirements may result in my provider choosing to stop writing opioid prescriptions for me. Withdrawal from the medications will be coordinated by the provider and may require specialist referrals.
12. I hereby agree that my provider has the authority to discuss my pain management with other health care professionals and my family members when it is deemed medically necessary in the provider's judgment.

Patient Signature: _____

# APPENDIX D

## PRESCRIBING CONTROLLED SUBSTANCES

Any physician or authorized practitioner in the VA system who prescribes controlled substances is bound by a set of regulations established by the VHA as well as by applicable Federal Laws. The Drug Enforcement Agency (DEA) is the Federal agency responsible for enforcing both the provisions of the Controlled Substances Act (CSA) and applicable regulations from the Code of Federal Regulations (CFR).

Note: Physicians and practitioners who are not employed in the Federal sector should consult with their individual State authority to determine whether there are State-level laws that cover the prescribing of controlled substances.

### Federal Regulations

The DEA, in a Drug Policy Briefs and Background paper (http://www.usdoj.gov/dea/pubs/csa.html), provides a useful introduction to the CSA:

> "The Controlled Substances Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, is the legal foundation of the government's fight against the abuse of drugs and other substances. This law is a consolidation of numerous laws regulating the manufacture and distribution of narcotics, stimulants, depressants, hallucinogens, anabolic steroids, and chemicals used in the illicit production of controlled substances.
>
> "The CSA places all substances that are regulated under existing Federal law into one of five schedules. This placement is based upon the substance's medicinal value, harmfulness, and potential for abuse or addiction. Schedule I is reserved for the most dangerous drugs that have no recognized medical use, while Schedule V is the classification used for the least dangerous drugs. The act also provides a mechanism for substances to be controlled, added to a schedule, decontrolled, removed from control, rescheduled, or transferred from one schedule to another.
>
> "The CSA also creates a closed system of distribution for those authorized to handle controlled substances. The cornerstone of this system is the registration of all those authorized by the DEA to handle controlled substances. All individuals and firms that are registered are required to maintain complete and accurate inventories and records of all transactions involving controlled substances, as well as security for the storage of controlled substances."

The DEA website maintains a current list of scheduled substances at http://www.usdoj.gov/dea/pubs/scheduling.html. An additional resource for the clinician is the U.S. Department of Justice's Drug Enforcement Administration Diversion Control Program website at http://www.deadiversion.usdoj.gov/. Clinicians can obtain online versions of the CSA and CFR at this site, as well as registration forms and additional information for physicians.

### Veteran's Health Administration Regulations

The Department of Veterans Affairs has published a Handbook covering controlled substance regulations (1997). This Handbook is available at http://www.va.gov/publ/direc/health/handbook/1108-1.htm. The Handbook "defines procedures for the Department of Veterans Affairs (VA) accountability of all controlled substances and compliance with Drug Enforcement Administration (DEA) Regulations."

As noted in the Handbook, "VA maintains perpetual inventory of all controlled substances. These items will consist of the drugs and other substances by whatever official name, common or usual name, chemical name, or brand name designated, listed in Title 21 Code of Federal Regulations (CFR) Part 1300:

(1) Schedule II drugs are found in 21 CFR 1308.12,
(2) Schedule III drugs are found in 21 CFR 1308.13,
(3) Schedule IV drugs are found in 21 CFR 1308.14, and
(4) Schedule V drugs are found in 21 CFR 1308.15."

Regulations concerning prescribing and labeling controlled substances are as follows:

- All prescriptions for controlled substances will be dated as of and signed on the day when issued and bear the full name and address of the patient, and the name, address, and DEA registration number of the practitioner. Prescriptions should not be filled if they are more than 7 days old when presented.

- An intern, resident, mid-level practitioner, foreign-trained physician, physician, or dentist on the staff of a VA facility exempted from registration (21 CFR 1301.24) will include on all prescriptions issued the registration number of the VA facility and the special internal code number assigned by the VA facility in lieu of the registration number of the practitioner required by law (21 CFR 1306.05b). Each written prescription will have the name of the physician or authorized practitioner stamped, typed, or hand-printed on it, as well as the signature of the physician or authorized practitioner.
- The label of any drug listed as a "Controlled Substance" in Schedule II, III, IV, or V of the Controlled Substances Act will, when dispensed to or for a patient, contain the following warning: "CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed."

The clinician may wish to consult the Handbook for further details on controlled substance regulations in the VA system.

# APPENDIX E

## Drug Tables

**Table E1. Use of Short-Acting, Orally Administered Opioids in OPIOID-NAIVE Adults (70 kg)**

| Short-Acting Opioid† | Initial Dosage | Dosage Titration | Analgesic Onset (min), Peak (min), Duration (h) | Dosing in Special Populations |
|---|---|---|---|---|
| Codeine (alone or in combination with APAP or ASA) | 30 mg p.o. q 4 to 6 h | Increase dose as needed and tolerated to a maximum of 360 mg/d (4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics)<br>Ceiling effect occurs at doses > 60 mg/dose | 15 to 30<br>30 to 60<br>4 to 6 | Elderly or debilitated – use with caution<br>Hepatic dysfunction – conversion to active metabolite (morphine) may be reduced in patients with cirrhosis; avoid use in patients with liver disease<br>Renal dysfunction – use lower dosage or an alternative analgesic |
| Hydrocodone (in combination with APAP, ASA, or IBU) | 5 to 10 mg p.o. q 4 to 6 h | Increase dose as needed and tolerated<br>Maximum dose:<br>60 mg/d (4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics) for hydrocodone + APAP combination,<br>or<br>37.5 mg/d (1000 mg/d IBU) for hydrocodone + IBU combination | 15 to 30<br>30 to 60<br>4 to 8 | Elderly or debilitated – use with caution; start at low end of dosing range<br>Hepatic / Renal dysfunction – use with caution |
| Hydromorphone | 2 mg p.o. q 4 to 6 h | Individually titrate as needed and tolerated; doses ≥ 4 mg q 4 to 6 h may be necessary | 15 to 30<br>30 to 60<br>4 to 6 | Elderly or debilitated – use with caution, starting at low end of dosing range<br>Hepatic / Renal dysfunction – use with caution |

## Table E1. Use of Short-Acting, Orally Administered Opioids in Opioid-Naive Adults (70 kg) continued

| Short-Acting Opioid† | Initial Dosage | Dosage Titration | Analgesic Onset (min), Peak (min), Duration (h) | Dosing in Special Populations |
|---|---|---|---|---|
| Morphine | 10 to 30 mg p.o. q 4 h | Individually titrate as needed and tolerated | 15 to 60<br>60 to 90<br>2 to 6 | Elderly or debilitated – give with extreme caution; use lower dose<br>Hepatic dysfunction – use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 h) and bioavailability is increased<br>Renal dysfunction – reduce dose or, if severe renal impairment exists, avoid use |
| Oxycodone (alone or in combination with APAP or ASA) | 5 mg p.o. q 6 h | Increase dose as needed and tolerated for combination products, maximum dose is limited by APAP or ASA content (4000 mg/d for both; 2000 mg/d APAP in chronic alcoholics) | 10 to 15<br>30 to 60<br>3 to 6 | Elderly or debilitated– reduce dosage<br>Hepatic / Renal – use with caution |
| Propoxyphene (alone or in combination with APAP) | HCl:<br>65 mg p.o. q 6 to 8 h<br>Napsylate:<br>100 mg p.o. q 6 to 8 h | Increase dose as needed and tolerated<br>Maximum daily dose is 390 mg/d for HCl salt and 600 mg/d for napsylate salt<br>(Maximum daily dose of APAP: 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics) | 15 to 60<br>120 to 180<br>4 to 6 | Co-ingestion of alcohol or other CNS depressants with moderate (6 to 20 capsules or tablets) overdoses of propoxyphene has been associated with serious toxicity including death<br>Elderly or debilitated – use is not recommended in elderly; half-life of propoxyphene and norpropoxyphene may be markedly prolonged (36 and 53 h, respectively) in elderly patients. Use with caution in debilitated patients.<br>Hepatic disease – increased bioavailability of propoxyphene; reports of hepatotoxicity; avoid use in patients with liver disease<br>Renal dysfunction – propoxyphene and norpropoxyphene accumulate in renal insufficiency; may result in respiratory or CNS depression, neurotoxicity, or cardiotoxicity; avoid use |
| Tramadol (alone or in combination with APAP) | 25 mg p.o. q a.m. | Increase by 25 mg as separate doses every 3 d to 100 mg/d (25 mg q 6 h)<br>Subsequent increments of 50 mg/d may be made every 3 d to 200 mg/d (50 mg q 6 h)<br>After titration, may give 50 to 100 mg q 4 to 6 h<br>Maximum daily dose: 400 mg/d<br>(Maximum 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics) | < 60<br>~120 to 240<br>3 to 6 | Elderly or debilitated – in elderly patients >75 yr give < 300 mg/d in divided doses. Use with caution in debilitated patients.<br>Hepatic dysfunction – decrease dosage to 50 mg q 12 h in patients with cirrhosis<br>Renal dysfunction (CrCl < 30 ml/min) – increase dosing interval to 12 h and decrease maximum daily dose to 200 mg. Dialysis patients can receive their regular dose on the day of dialysis (< 7% of a dose is removed by hemodialysis) |

*Sources: Ortho-McNeil, Tylenol with codeine package insert (2000); Ortho-McNeil, Ultram package insert (2001); Drug Facts and Comparisons (2002); Endo, Percocet, Percodan, and Zydone package inserts (2001); Purdue, MSIR package insert (2001) and OxyIR package insert (2000); Michalets (1998); Davis and Homsi (2001)*

*APAP = Acetaminophen; ASA = Aspirin (acetylsalicylic acid); IBU = Ibuprofen; MAOI = Monoamine oxidase inhibitor*

†*Check local formulary for available formulations.*

## Table E2. Use of Long-Acting Opioids in OPIOID-NAIVE Adults (70 kg)

| Long-Acting Opioid† | Initial Dosage | Dosage Titration | Analgesic Onset (min), Peak (min), Duration (h) | Dosing in Special Populations |
|---|---|---|---|---|
| Fentanyl Transdermal System | 25 mcg/h t.d. q 72 h | Increments should be based on supplemental opioid doses, using a ratio of 25 mcg/h t.d. fentanyl for every 90 mg/24 h of supplemental oral morphine equivalent<br>Make increments at least 3 d after initial dose then not more often than q 6 d thereafter as necessary | 12 to 18 (h)<br>24 to 72 (h)<br>48 to 72 | Elderly or debilitated – avoid initiation at doses > 25 mcg/h unless patient is already taking > 135 mg oral morphine or equivalent. In elderly patients, clearance of i.v. fentanyl may be greatly decreased; relevance to t.d. fentanyl is unknown; use reduced dose<br>Hepatic / Renal dysfunction – insufficient information; use with caution<br>Patients with fever – increased body temperature may increase release of fentanyl from the t.d. system; monitor patients for opioid adverse effects and modify dosage as necessary |
| Levorphanol | 2 mg p.o. q 6 to 8 h<br>Longer initial dosing intervals (e.g., q 12 h) may be possible | Maximum initial individual dose: 3 mg<br>Maximum initial total daily dose: 6 to 16 mg/d<br>Individually titrated as needed and tolerated<br>Allow at least 36 to 72 h before making dosage increments | 30 to 60<br>60 to 120<br>4 to 14 (dose-dependent) | Elderly or debilitated – reduce dose; in elderly, consider reducing dose by 50% or more<br>Hepatic / Renal dysfunction – no pharmacokinetic data; use with caution<br>Respiratory disease / Respiratory depressants – reduce initial dose by ≥ 50%<br>Patients taking MAOIs – use with MAOIs is not recommended (even though no interaction between levorphanol and MAOIs has been reported) |
| Methadone | 2.5 mg p.o. q 6 to 8 h | Increments of 2.5 mg q 8 h may be made every 5 to 7 d | 30 to 60<br>—<br>4 to 12<br>Analgesic duration increases with continued use and cumulative effects | Elderly or debilitated – reduce dosage; in elderly, clearance may be decreased<br>Hepatic dysfunction – in patients with stable chronic liver disease or mild to moderate hepatic dysfunction, no dosage adjustments required<br>Renal dysfunction – methadone and its metabolites do not accumulate in patients with renal failure; however, dosage reduction by up to 50% is recommended in end-stage renal failure or dialysis patients |

## Table E2. Use of Long-Acting Opioids in Opioid-Naive Adults (70 kg) continued

| Long-Acting Opioid† | Initial Dosage | Dosage Titration | Analgesic Onset (min), Peak (min), Duration (h) | Dosing in Special Populations |
|---|---|---|---|---|
| Morphine Controlled Release (CR) | 15 mg p.o. q 12 h | Total daily increments of < 30 to 40 mg/d may be made q 2 d | 30 to 60<br>30 to 60<br>8 to 12 | Elderly or debilitated – use with caution and at lower dose<br>Hepatic dysfunction – use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 h) and bioavailability is increased<br>Renal dysfunction – reduce dose or, if severe renal impairment exists, avoid use |
| Morphine Sustained Release (SR) | 15 mg p.o. q 12h<br>20 mg p.o. q 24h | | 8 to 24 | |
| Morphine Extended Release (ER) | 30 mg p.o. q 24 h | | | |
| Oxycodone Controlled Release | 10 mg p.o. q 12 h | May increase to 20 mg q 12 h after 1 or 2 d<br>Thereafter, the total daily dose may be increased by 25% to 50% of the current dose every 1 or 2 d | 30 to 60<br>90 to 180<br>8 to 12 | Elderly or debilitated patients – reduce initial dosage to 1/3 to 1/2 of the usual dose<br>Hepatic dysfunction – reduce initial dose to 1/3 to 1/2 of the usual dose and use with caution<br>Renal dysfunction – plasma concentrations of oxycodone are increased about 50% in patients with CrCl < 60 ml/min; dose conservatively, adjusting dosage according to clinical situation |

*Sources: ICN, Levo-Dromoran package insert (1995); Roxane Laboratories Inc., Levorphanol tartrate package insert (2000); Janssen Pharmaceutica, Duragesic package insert (2001) CPSO,* Evidence-based recommendations for medical management of chronic non-malignant pain *(2000); Drug Facts and Comparisons (2002);Purdue Pharma, OxyContin package insert (2001); Purdue Pharma, MS Contin package insert (2000); American Pain Society,* Principles of analgesic use in the treatment of acute pain and cancer pain *(1999)*

*P.o. = Per os (orally); t.d. = Transdermally*

†*Check local formulary for available formulations.*

*THIS GUIDELINE DOES NOT RECOMMEND THE USE OF LONG-ACTING OPIOID AGONISTS FOR AS-NEEDED (P.R.N.) ADMINISTRATION.*

## Table E3. Equianalgesic Opioid Conversion Ratios for Patients Previously Receiving Other Opioids

| Opioid Agent | Estimated Equianalgesic Dose (mg)* | Initial Conversion Dose (Not Equianalgesic)† |
|---|---|---|
| Codeine | 180 to 200 p.o.‡ | 30 mg q 4 to 6 h |
| Fentanyl | — (transdermal) | For converting ONLY to fentanyl from another opioid, use about 25 mcg/h fentanyl transdermally for every 90 mg of oral morphine or equivalent (see Table E4: Initial Fentanyl Transdermal Dosage) |
| Hydrocodone | 30 p.o. | 50% to 67% of estimated oral equianalgesic dose |
| Hydromorphone | 7.5 p.o. | 50% to 67% of estimated oral equianalgesic dose |
| Levorphanol | 4 p.o. acute<br>1 p.o. chronic | 50% to 67% of estimated oral equianalgesic dose |
| Methadone | 20 p.o. acute<br>2 to 4 p.o. chronic | Methadone-to-morphine dosage proportion (%) is dependent on morphine-equivalent dose of previous opioid<br>For gradual conversion to methadone:<br>**Oral morphine** — **Methadone**<br>< 200 mg/d — 5 mg q 8 h<br>200 to 500 mg/d — ~7% of oral morphine-equivalent dose, given in divided doses q 8 h<br>> 500 mg/d — See Appendix F: Methadone Dosing Recommendations for Treatment of Chronic Pain<br>Consider consultation with a pain specialist, clinical pharmacist, or other practitioner who has experience with using methadone for chronic pain |
| Morphine | 30 p.o. | 50% to 67% of estimated oral equianalgesic dose |
| Oxycodone | 15 to 20 p.o.§ | 50% to 67% of estimated oral equianalgesic dose |
| Propoxyphene | 100 to 130 p.o.‡ | HCl: 65 mg q 6 to 8 h<br>Napsylate: 100 mg q 6 to 8 h |
| Tramadol | 100 to 150 p.o.‡ | 25 mg q.a.m. |

*Sources: American Pain Society,* Principles of analgesic use in the treatment of acute pain and cancer pain *(1999); CPSO,* Evidence-based recommendations for medical management of chronic non-malignant pain *(2000); Drug Facts and Comparisons (2002)*

* *Many other equianalgesic dosing tables are available that may provide equivalent doses different from those shown here.*

† *The initial dose of the new drug applies to patients who are not tolerant to the new opioid and should be given 50% to 67% of the calculated dose for all potent opioids except fentanyl and methadone to allow for incomplete cross-tolerance (the new drug may have more relative analgesic efficacy and more adverse effects). For methadone, use dosage proportions (%) based on the morphine-equivalent dose of previous opioid (also see Appendix F: Methadone Dosing Recommendations for Treatment of Chronic Pain). Initial doses should be individualized. The patient's medical condition; the potency, dose, and type of previous opioid; the patient's degree of opioid exposure and tolerance; the patient's past analgesic response and adverse experiences; and the accuracy and reliability of opioid conversion factors may all influence the choice of starting dose. For fentanyl, see Table E4.*

‡ *When converting from weak opioid analgesics to stronger opioids, use the recommended initial doses of the new opioid for opioid-naive patients (see Table E1 and Table E2). Dose of tramadol should NOT be considered equianalgesic to the doses of pure agonists.*

§ *Exceeds recommended initial dose (oxycodone 5 mg)*

## Opioid Conversion Instructions

1. Determine the total 24-hour dose of the current opioid.
2. Using the estimated equianalgesic dose, calculate the equivalent dose of new analgesic for the desired route of administration.
3. When converting to a different opioid, for most agents, the starting conversion dose of the new opioid should be 50% to 67% of the equianalgesic dose because of incomplete cross-tolerance. (For methadone and fentanyl, see conversion doses in Table E3).
4. Take the 24-hour starting dose of the new opioid and divide by the frequency of administration to give the new dose for the new route.
5. Consider rescue opioid therapy during the conversion process.

**Examples**

*Conversion to methadone*

Patient is receiving a total of 360 mg oral morphine in a 24-hour period.

1. From the equianalgesic table, we determine that the initial conversion dose of methadone is about 7% of the oral morphine-equivalent dose. The initial conversion dose would be about 25 mg per day.
2. The recommended frequency of administration for methadone is q 8 h (3 doses per day).
3. Consulting the local drug formulary, we find that methadone is available in 5-mg scored tablets. The starting dose of methadone would be 7.5 mg q 8 h (22.5 mg/d).
4. Titrate dose at appropriate intervals depending on response and adverse effects.

*Conversion to oxycodone CR*

Patient is receiving a total of 360 mg oral morphine in a 24-hour period.

1. From the equianalgesic table, we calculate that the estimated equianalgesic dose of oxycodone is 180 to 240 mg per day.
2. The initial conversion dose of oxycodone is 50% to 67% of 180 to 240 mg per day or about 90 to 160 mg per day.
3. The recommended frequency of administration for oxycodone is every 12 hours (2 doses per day).
4. Consulting the local drug formulary, we find that oxycodone is available in 10-, 20-, 40-, and 80-mg controlled-release tablets. The starting dose of oxycodone controlled-release would be 40 to 80 mg q 12 h. To be conservative, a dose of 40 mg q 12 h (80 mg/d) is selected.
5. Titrate dose at appropriate intervals depending on response and adverse effects.

## Table E4. Initial Fentanyl Transdermal Dosage (only for converting another opioid to fentanyl)

| Oral 24-Hour Morphine (mg/d) | Fentanyl Transdermal (mcg/h) |
|---|---|
| 45–134 | 25 |
| 135–224 | 50 |
| 225–314 | 75 |
| 315–404 | 100 |
| 405–494 | 125 |
| 495–584 | 150 |
| 585–674 | 175 |
| 675–764 | 200 |
| 765–854 | 225 |
| 855–944 | 250 |
| 945–1034 | 275 |
| 1035–1124 | 300 |

*Source: Drug Facts and Comparisons (2002)*

Note: **Do not use this table to convert from fentanyl transdermal system to other opioid analgesics because these conversion dosage recommendations are conservative.** Use of this table for conversion from fentanyl to other opioids can overestimate the dose of the new agent and may result in overdosage of the new agent.

## Table E5. Recommendations for Supplemental Opioid Therapy

| Type of Therapy | Description of Pain Episode | Recommendation | General Guidelines for Supplemental Opioid Therapy |
|---|---|---|---|
| Rescue | Insufficient analgesia during dosage titration | In patients being started on a new opioid, consider giving rescue medication<br>Rescue therapy is often used when pain is severe or escalating | Use supplemental short-acting opioid, non-opioid, or a combination of both agents on an as-needed basis<br>When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10% of the daily opioid dose as needed<br>When using combination products, do not exceed maximum recommended doses of acetaminophen (4000 mg), aspirin (4000 mg), or ibuprofen (1000 mg)<br>Encourage the use of nonpharmacologic modalities<br>Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence |
| Breakthrough pain | Unpredictable exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid | Controversial, not routinely recommended<br>If necessary, use breakthrough pain medications sparingly | |
| Incident pain | Predictable, activity-related exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid | Many patients taking long-acting opioid analgesics may need supplemental analgesia for incident pain (e.g., 8 to 12 doses per month of short-acting opioid preparation) | |

# APPENDIX F
## METHADONE DOSING RECOMMENDATIONS FOR TREATMENT OF CHRONIC PAIN

**Overview**

- Although methadone has unique pharmacokinetic and pharmacodynamic properties, the general principles of dosing methadone are similar to those of other opioids.
- Methadone is most easily titrated by using small initial doses or adjusting the initial dose according to the previous opioid dose.
- A number of methods are available for titrating methadone using conversion ratios, as detailed below. However, titration should be based on patient response and not solely based on equianalgesic dosing tables.
- Consultation with a pain specialist, clinical pharmacist, or other practitioner who has experience with using methadone for chronic pain is recommended if questions arise about dosing or titrating methadone.

**Background**

While methadone has gained increasing acceptance as an alternative to morphine for treatment of moderate to severe pain, a number of authors have cautioned clinicians about the complexities of dosing methadone or have suggested the drug be prescribed by practitioners with relevant experience in an adequately monitored setting. Significant toxicity has occurred particularly when dosage increments were made too frequently, conversion doses were too high, or dosing intervals were too close. Accruing experience, however, suggests that methadone can be safely used when initial doses are small, conversion ratios are adjusted to the previous opioid dose, and dosage is slowly titrated to patient response. The general principles of dosing methadone are similar to those of other opioids.

The pharmacokinetic and pharmacodynamic properties of methadone are complex and incompletely documented. Although methadone may have a long elimination half-life (range of mean/medians among studies: 3 to 128 hours in healthy volunteers, opiate addicts, patients with chronic pain, and patients with acute pain), the elimination half-life does not necessarily reflect duration of analgesia. Patients may require dosing intervals of 6 hours to achieve adequate pain relief, although repeated oral administration of methadone for cancer pain may lead to progressively longer dosing intervals. As a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. Patients need to be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased. However, once a stable dosing is established, follow-up can be as clinically indicated. With a 3-day phased conversion from morphine to methadone, the analgesic effects have taken a median of 5 days (range: 4 to 13 days) to stabilize.

It is important to note that the equianalgesic conversion ratios between methadone and other opioids are imprecise.

**Summary**

- Methadone is a synthetic opioid analgesic with similar adverse effects to other opioids.
- Duration of action is usually 6 hours or longer.
- Methadone is the only long-acting opioid available as an oral solution.
- Long half-life and drug accumulation can lead to delayed toxicity (e.g., on days 2 to 5).
- The analgesic effects of methadone may take about 1 to 2 weeks to stabilize.
- The equianalgesic dose of methadone in repetitive dosing is much smaller (1/5 to 1/10) than that suggested by single-dose studies.
- Initial doses of methadone should be small and adjusted to the previous opioid dose, using smaller methadone-to-morphine-equivalent conversion ratios (%) the larger the previous morphine-equivalent dose.
- As with other opioids, methadone requires close patient monitoring for analgesic and adverse effects.

## Table F1. Points To Consider about Equianalgesic Conversion Ratios

- A number of equianalgesic dosing tables underestimate the potency of methadone.[†]
- Conversion ratios in many equianalgesic dosing tables do not apply to repeated doses of opioids.
- The morphine- or hydromorphone-to-methadone conversion ratio increases (i.e., the potency of methadone increases) as the previous dose of morphine or hydromorphone increases.[‡]
- Conversion ratios may not be bi-directional (i.e., the morphine-to-methadone conversion ratio may not be the same as the methadone-to-morphine ratio).[§]
- There may be large interpatient variability in the equianalgesic conversion ratio; a single ratio may not be applicable to all patients.[§]
- The use of high but ineffective doses of previous opioid may result in overestimation of the equivalent dose of methadone.
- The relative analgesic potency ratio of oral to parenteral methadone is 2:1; however, confidence intervals are wide.[‖]

[†] Management of Cancer Pain*, Clinical Practice Guidelines, AHCPR (1994);* Cancer pain: a monograph on the management of cancer pain*, Health & Welfare Canada (1984); Twycross (1990); Levy (1985)*

[‡] *The oral-morphine-to-oral-methadone conversion ratio may be unexpectedly much higher in patients who previously received very high doses of morphine.*

[§] *Bruera (1999)*

[‖] *Estimated ratio based on single-dose, double-blind, double-dummy, cross-over studies in patients with moderate to severe cancer pain.*

The present dosing recommendations are provided to offer guidance on dosing methadone in the treatment of patients with chronic non-cancer pain (CNCP) or chronic cancer pain, particularly when converting from another opioid to methadone. If in doubt, a practitioner should consult a pain management specialist, clinical pharmacist, or another practitioner who has the relevant knowledge.

### Dosing Strategies

Recommendations for the use of methadone in the management of CNCP are extrapolated from studies involving mostly patients with cancer pain.

## Table F2. Dosing Recommendations for Patients Receiving Codeine Preparations or No Previous Opioids

| Dosing Strategy | Initial MET Dose | Increments | Comments |
|---|---|---|---|
| **Gradual titration**<br>(For CNCP and situations necessitating less frequent monitoring)[44] | 2.5 mg q 8 h | 2.5 mg q 8 h every 5 to 7 d | As a general rule, *start low* and *go slow.* |
| **Faster titration**<br>(For cancer pain and situations where frequent monitoring is possible) | 2.5 mg q 6 or 8 h | 2.5 mg q 6 or 8 h as often as every day over about 4 d | |

*The dosing recommendations for gradual titration were modified with permission from* Evidence-Based Recommendations for Medical Management of Chronic Non-Malignant Pain*, College of Physicians and Surgeons of Ontario, November 2000. All doses refer to oral administration.*

*CNCP = Chronic non-cancer pain; MET = Methadone*

## Table F3. Dosing Recommendations for Patients Previously Receiving Other Opioids

**Gradual Conversion** (For CNCP and patients monitored less frequently)

| MOR-E [mg/d] | Calculated MET Dose [mg /d] | Initial MET Dose | Increment |
|---|---|---|---|
| < 200 | 15 mg | 5 mg q 8 h | Increase by calculated MET dose every 5 – 7 d |
| 200 – 500 | ~ 7% of MOR-E * | Calculated MET dose given in divided doses q 8 h | Increase by calculated MET dose every 5 – 7 d |
| >500 | ~ 7% of MOR-E * | 1/3 of calculated MET dose given in divided doses q 8 h | Add 1/3 of calculated MET dose every 5 d<br>Decrease previous opioid by 1/3 every 5 d<br>(Complete conversion period = 15 days) |

* Calculation of MET dose based on oral morphine-equivalent [MOR-E] doses:

| | | | |
|---|---|---|---|
| Methadone | [MET] | 2 mg | *Examples:* |
| Morphine | [MOR] | 30 mg | 250 mg/d MOR = 250 x 2 /30 = 17 mg/d MET ~ 5 mg q 8 h |
| Hydromorphone | [HMO] | 8 mg | 60 mg/d HMO = 60 x 2 / 8 = 15 mg/d MET = 5 mg q 8 h |
| Oxycodone | [OXY] | 15 mg | 120 mg/d OXY = 120 x 2 /15 = 16 mg/d MET ~ 5 mg q 8 h |
| | | | 600 mg/d MOR = 600 x 2/30 = 40 mg/d MET<br>1/3 of 40 mg/d = 13 mg/d or about 15 mg/d<br>Give:<br>MET 5 mg q 8 h + MOR 400 mg/d (in divided doses) x 5 d<br>MET 10 mg q 8 h + MOR 200 mg/d (in divided doses) x 5 d<br>MET 15 mg q 8 h + discontinue MOR |

**Rapid Conversion** (For cancer pain and patients monitored frequently) [2,3,5,11,12,45,46]

| MOR-E [mg/d] | MET-to-MOR-E Ratio [%] | Initial MET dose | Increment |
|---|---|---|---|
| < 200 | 10% – 30% | Calculated daily MET dose in divided doses q 8 h<br>(up to a maximum 50 mg q 8 h) | **Phased Conversion:** Replace 1/3 of MOR-E dose with calculated dose of MET every day (complete conversion in 3 days)<br>**Rapid (Stop-and-Go):** Discontinue MOR-E and start calculated dose of MET on day 1 |
| 200 – 500 | 10% – 20% | | |
| 500 – 1000 | 5% – 10% | | |
| > 1000 | 5% or less | | |

*Example of Phased Conversion:*
600 mg/d MOR = 30 to 60 mg/d MET (or ~ 45 mg/d)
1/3 of MET dose = 10 to 20 mg/d (or ~ 15 mg/d)
Day 1: MET 5 mg q 8 h + MOR 400 mg/d (in divided doses)
Day 2: MET 10 mg q 8 h + MOR 200 mg/d (in divided doses)
Day 3: MET 15 mg q 8 h + discontinue MOR

1. *For the most conservative approach, use 5% MET/MOR-E (or less with very high MOR-E doses) to calculate the initial MET dose irrespective of the previous MOR-E dose.*
2. *Titrate MET day by day according to patient's symptoms and the number of rescue doses administered.*
3. *Smaller MET-to-MOR-E conversion ratios (%) should be used the larger the previous MOR-E dose.*

**CNCP = Chronic non-cancer pain HMO = Hydromorphone MET = Methadone**
**MOR = Morphine MOR-E = Morphine-equivalent OXY = Oxycodone**

It is important to note that various dosing methods have been used (including a patient-controlled regimen) and are still evolving. Two dosing strategies have been prospectively studied, but no clinical trials comparing systematic dosing methods have been performed. A literature search (PubMed 1966 to 2001) identified only a small case series that discussed methadone dosing during the treatment of CNCP. The lack of prospective and comparative studies highlights the need to carefully individualize the dosing regimen of methadone, as is done with other opioids.

As a general rule, smaller methadone-to-morphine conversion proportions (%) should be used the larger the previous morphine-equivalent dose, remembering that precise conversions from another opioid to methadone are impossible. Disproportionately smaller methadone doses may be required with the larger morphine doses. However, it is important to remember that the equianalgesic conversion ratio is only one part of the process of properly dosing methadone and other opioids.

For inadequately treated pain during titration, a short-acting opioid preparation (such as acetaminophen with codeine, oxycodone with or without acetaminophen, or immediate-release morphine) may be used as necessary. Keep in mind that the use of supplemental opioid medications in patients with CNCP is controversial. If opioid medications for breakthrough pain (BTP) are indicated following titration to a stable methadone dose in a patient with CNCP, they should be used sparingly. Methadone has been used for inadequately treated pain during titration (in doses 10% to 30% of the calculated daily methadone dose up to 3 to 8 doses per day as needed); however, the short-acting opioids are generally preferred to avoid drug accumulation.

**Special patient populations**

Patients 65 years and older may have a decreased clearance of methadone. In patients with stable chronic liver disease, no dosage adjustments appear to be necessary. Methadone and its metabolites do not accumulate in patients with renal failure. The two prospective studies on methadone dosing strategies excluded patients with liver or renal disease. Use extra caution when dosing any opioid in all of these patient populations.[1]

[1] *For patients with liver or renal disease, special consideration can be given locally to use an alternative opioid at the discretion of the care team or provider.*

**COMMENTS**

- Once a stable analgesic dose is reached, dosing intervals may be extended to 8 to 12 hours or longer.
- Provide careful dose titration until adequate pain relief is achieved or adverse effects limit further dose escalation.
- Absence of a graded analgesic response (in CNCP) suggests that the patient's pain may not be "opioid-responsive."
- Patients should be closely monitored, at least once weekly during titration and at least once a month during maintenance.
- Patients should be warned about potential adverse effects (drowsiness, respiratory depression) and the possibility that analgesic and adverse effects may continue to evolve during the week after each dose adjustment.
- If drowsiness develops, patients (or family member) should contact the provider to obtain advice about further dosing.
- Use additional caution with elderly patients (65 years and older); patients with liver, renal, or pulmonary disease; debilitated patients; and patients previously receiving high doses of opioid. Patients who cannot be monitored at home may be considered for inpatient titration of methadone.

**Patient education**

- Explain to patients that the initial dose may not provide optimum pain relief but that the starting dose is chosen in order to reduce the chance of adverse effects. A pain and pain medicine diary should be kept.
- Reassure patients that the dose will be titrated to achieve adequate analgesia.
- When applicable, explain the reason for and how to use the short-acting opioid during methadone dose titration.
- Advise patients that the effects of methadone will increase over at least one week following a dosage increment. Pain relief during the last few days of that week will be greater than at the first few days of the week.

- Remind patients about the need for and the frequency of monitoring during the titration and maintenance periods. Provide patients with instructions on what to do if they develop increasing or intolerable adverse effects.
- Advise patients to avoid abrupt discontinuation of their opioid medication without first consulting their physician. Educate patients about withdrawal symptoms.
- Since patients may become concerned about the social stigma associated with the use of methadone for treatment of opioid dependence, reassure them that methadone is also an accepted pain medication and that they are not "addicts" because they are taking methadone for pain control. Explain the difference between addiction and dependence.[2]

[2] *For more information on the definitions of addiction and dependence, see the web-based educational program for VA employees entitled* Opioids in the Management of Acute and Chronic Pain; *available at: http://vaww.sites.lrn.va.gov/pain/opioids/ or reference 51.*

# APPENDIX G

## Acronym List

| | |
|---|---|
| BID | Bis In Die (Latin: twice a day) |
| BM | Bowel Movement |
| CNS | Central Nervous System |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPAP | Continuous Positive Airway Pressure |
| CPG | Clinical Practice Guideline |
| CR | Controlled-Release |
| CSA | Controlled Substances Act |
| DC | Discontinue |
| DEA | Drug Enforcement Administration |
| DoD | Department of Defense |
| DSM-IV | Diagnostic and Statistical Manual – Version IV |
| EMG | Electromyography |
| ER | Extended Release |
| GI | Gastrointestinal |
| JCAHO | Joint Commission on Accreditation of Healthcare Organizations |
| LBP | Low Back Pain |
| MAOI | Monoamine Oxidase Inhibitors |
| NRS | Numerical Rating Scale |
| NSAID | Non-Steroid Anti-Inflammatory Drug |
| PHN | Postherpetic Neuralgia |
| PO | Per Os (Latin: by mouth, orally) |
| PRN | Pro Re Nata (Latin: as needed) |
| RCT | Randomized Controlled Trial |
| SR | Sustained-Release |
| SUD | Substance Use Disorder |
| TENS | Transcutaneous Electrical Nerve Stimulation |
| TID | Ter In Die (Latin: three times a day) |
| UDS | Urine Drug Screen |
| VA | Veterans Administration |